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[54] **STABILIZED MICROBUBBLE COMPOSITIONS**

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Related U.S. Application Data

[63] Continuation of Ser. No. 99,951, Jul. 30, 1993, abandoned.

[51] **Int. Cl.**[6] **A61K 49/00**

[52] **U.S. Cl.** **424/9.52**; 424/9.5

[58] **Field of Search** 424/9.5, 9.51, 424/9.52

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[57] **ABSTRACT**

A microbubble preparation formed of a plurality of microbubbles comprising a first gas and a second gas surrounded by a membrane such as a surfactant, wherein the first gas and the second gas are present in a molar ratio of from about 1:100 to about 1000:1, and wherein the first gas has a vapor pressure of at least about (760–x) mm Hg at 37° C., where x is the vapor pressure of the second gas at 37° C., and wherein the vapor pressure of each of the first and second gases is greater than about 75 mm Hg at 37° C.; also disclosed are methods for preparing microbubble compositions, including compositions that rapidly shrink from a first average diameter to a second average diameter less than about 75% of the first average diameter and are stabilized at the second average diameter; kits for preparing microbubbles; and methods for using such microbubbles as ultrasound contrast agents.

52 Claims, No Drawings

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The foregoing description details certain preferred embodiments of the present invention and describes the best mode contemplated. It will be appreciated, however, that no matter how detailed the foregoing appears in text, the invention can be practiced in many ways and the invention should be construed in accordance with the appended Claims and any equivalents thereof.

What is claimed is:

1. A microbubble preparation, comprising:

an aqueous medium containing a plurality of microbubbles, said microbubbles comprising:

a generally spherical microbubble membrane;

a first gas and a second component contained within said membrane, wherein said second component comprises the vapor of a compound that is a liquid at 37° C. and 760 mm Hg but which has a vapor pressure of at least 75 mm Hg at 37° C., wherein the first gas and the second component are respectively present in a molar ratio of about 1:100 to about 1000:1, with the proviso that said first gas and said second component are not water vapor.

2. The preparation of claim 1, wherein said second component comprises a fluorocarbon and said first gas is a nonfluorocarbon.

3. The preparation of claim 2, wherein said first gas comprises nitrogen, oxygen, carbon dioxide, or a mixture thereof.

4. The preparation of claim 2, wherein:

said microbubbles are in a liquid medium and have a first average diameter;

the ratio of said first gas to said second component in said microbubbles is at least 1:1; and

said microbubbles are adapted to shrink in said medium as a result of loss of said first gas through said membrane to a second average diameter of less than about 75% of said first diameter and then remain stabilized at or about said second diameter for at least about 1 minute as a result of a gas osmotic pressure differential across said membrane.

5. The preparation of claim 4, wherein said liquid medium contains gas or gases dissolved therein with a gas tension of at least about 700 mm Hg, wherein said first diameter is at least about 5 μm, and wherein the tension of the gas or gases dissolved in said medium is less than the pressure of the same gas or gases inside said microbubbles.

6. The preparation of claim 4, wherein said first diameter is at least about 10 μm and said second diameter is between about 1 μm and 6 μm.

7. The preparation of claim 1, wherein said second component has an average molecular weight at least about 4 times that of said first gas.

8. The preparation of claim 1, wherein said molar ratio of said first gas to said second component is from about 1:10 to about 500:1.

9. The preparation of claim 1, wherein said second component comprises a fluorocarbon and said first gas is a nonfluorocarbon.

10. The preparation of claim 9, wherein said second component comprises at least two fluorocarbons.

11. The preparation of claim 9, wherein said second component comprises a perfluorocarbon.

12. The preparation of claim 1, wherein both said first gas and said second component comprise fluorocarbons.

13. The preparation of claim 1, wherein said second component has a water solubility of not more than about 0.5 mM at 25° C. and one atmosphere, and wherein said first gas has a water solubility at least about 10 times greater than that of said second component.

14. The preparation of claim 1, wherein the permeability of the membrane to said first gas is at least about 5 times greater than the permeability of said membrane to said second component.

15. The preparation of claim 1, further comprising:

a liquid in said container in admixture with said microbubbles, wherein said container further comprises means for transmission of sufficient ultrasonic energy to said liquid to permit formation of said microbubbles by sonication.

16. The preparation of claim 15, wherein said means for transmission comprises a flexible polymer material having a thickness less than about 0.5 mm.

17. The preparation of claim 1, wherein said membrane is a surfactant.

18. The preparation of claim 17, wherein said surfactant comprises a non-Newtonian viscoelastic surfactant.

19. The preparation of claim 17, wherein said surfactant is a carbohydrate.

20. The preparation of claim 19, wherein said carbohydrate is a polysaccharide.

21. The preparation of claim 17, wherein said surfactant is a fatty acid ester of a sugar.

22. The preparation of claim 17, wherein said surfactant is sucrose stearate.

23. The preparation of claim 17, wherein said surfactant is a phospholipid.

24. The preparation of claim 1, wherein said membrane is solid or semi-solid.

25. The preparation of claim 1, wherein said membrane is a proteinaceous material.

26. The preparation of claim 25, wherein said proteinaceous material is albumin.

27. The preparation of claim 2, wherein:

said microbubbles have a first average diameter;

the ratio of said first gas to said second component in said microbubbles is at least 1:1; and

said microbubbles are adapted to shrink in blood in vivo as a result of loss of said first gas through said membrane to a second average diameter of less than about 75% of said first diameter and then remain stabilized at or about said second diameter for at least about 1 minute as a result of a gas osmotic pressure differential across said membrane.

28. The preparation of claim 27, wherein said first diameter is at least about 5 μm, and wherein the tension of the gas or gases dissolved in said blood is less than the pressure of the same gas or gases inside said microbubbles.

29. The preparation of claim 27, wherein said first diameter is at least about 10 μm and said second diameter is between about 1 μm and 6 μm.

30. The preparation of claim 27, wherein said second component has an average molecular weight at least about 4 times that of said first gas.

31. The preparation of claim 27, wherein said molar ratio of said first gas to said second component is from about 1:10 to about 500:1.

32. The preparation of claim 27, wherein said second component comprises a fluorocarbon and said first gas is a nonfluorocarbon.

33. The preparation of claim 32, wherein said second component comprises at least two fluorocarbons.

34. The preparation of claim 32, wherein said second component comprises a perfluorocarbon.

35. The preparation of claim 27 wherein both said first gas and said second component comprise fluorocarbons.

36. The preparation of claim 1, wherein said microbubbles contain as said first gas, or as said second component, or respectively as said first gas and said second component, gaseous perfluorobutane and perfluorohexane in a ratio from about 1:10 to about 10:1.

37. The preparation of claim 1, wherein said microbubbles contain as said first gas, or as said second component, or respectively as said first gas and said second component, gaseous perfluorobutane and perfluoropentane in a ratio from about 1:10 to about 10:1.

38. The preparation of claim 4, wherein said medium is aqueous.

39. A kit for use in preparing microbubbles, comprising:

a sealed container;

a liquid in said container;

a surfactant in said container; and

a fluorocarbon gas in said container, wherein said liquid, said surfactant, and said fluorocarbon gas are together adapted to form microbubbles upon the application of energy to the sealed container.

40. The kit of claim 39, further comprising

means in said container for permitting transmission of sufficient external ultrasonic energy to said liquid to form microbubbles in said container.

41. The kit of claim 40, wherein said means for transmission comprises a flexible polymer membrane having a thickness less than about 0.5 mm.

42. The kit of claim 39, further comprising:

a nonfluorocarbon gas in said container, wherein the molar ratio of said nonfluorocarbon gas to said fluorocarbon gas is from about 1:10 to about 1000:1, with the proviso that said nonfluorocarbon gas is not water vapor.

43. A kit for use in preparing microbubbles, comprising:

a container;

dried liquid-soluble void-containing structures in said container, said void-containing structures defining voids having an average diameter less than about 100 μm;

a liquid suitable for in vivo injection in which said void-containing structures are substantially soluble;

a gas in said voids, wherein said gas is the vapor of a non-aqueous material that is a liquid at 37° C.; and

a surfactant, wherein said void-containing structures, said gas, and said surfactant are together adapted to form microbubbles upon addition to said container of said liquid.

44. The kit of claim 43, wherein said void-containing structures comprise at least in part said surfactant.

45. The kit of claim 43, wherein said surfactant is a non-Newtonian viscoelastic surfactant.

46. The kit of claim 43, wherein said surfactant is a fatty acid ester of a sugar.

47. The kit of claim 43, wherein said surfactant is a phospholipid.

48. The kit of claim 43, wherein said void-containing structures are proteinaceous.

49. The kit of claim 43, wherein said void-containing structures are formed of a carbohydrate.

50. The kit of claim 43, wherein said gas is a fluorocarbon.

51. The kit of claim 43, wherein said gas comprises perfluorohexane.

52. The kit of claim 43, wherein said void-containing structures comprise spray dried microspheres.

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Attorney, Agent, or Firm—Knobbe, Martens, Olson & Bear

[57] **ABSTRACT**

A microbubble preparation formed of a plurality of microbubbles comprising a first gas and a second gas surrounded by a membrane such as a surfactant, wherein the first gas and the second gas are present in a molar ratio of from about 1:100 to about 1000:1, and wherein the first gas has a vapor pressure of at least about (760–x) mm Hg at 37° C., where x is the vapor pressure of the second gas at 37° C., and wherein the vapor pressure of each of the first and second gases is greater than about 75 mm Hg at 37° C.; also disclosed are methods for preparing microbubble compositions, including compositions that rapidly shrink from a first average diameter to a second average diameter less than about 75% of the first average diameter and are stabilized at the second average diameter; kits for preparing microbubbles; and methods for using such microbubbles as ultrasound contrast agents.

52 Claims, No Drawings

08/19/2003, EAST Version: 1.04.0000

The foregoing description details certain preferred embodiments of the present invention and describes the best mode contemplated. It will be appreciated, however, that no matter how detailed the foregoing appears in text, the invention can be practiced in many ways and the invention should be construed in accordance with the appended Claims and any equivalents thereof.

What is claimed is:

1. A microbubble preparation, comprising:

an aqueous medium containing a plurality of microbubbles, said microbubbles comprising:

a generally spherical microbubble membrane;

a first gas and a second component contained within said membrane, wherein said second component comprises the vapor of a compound that is a liquid at 37° C. and 760 mm Hg but which has a vapor pressure of at least 75 mm Hg at 37° C., wherein the first gas and the second component are respectively present in a molar ratio of about 1:100 to about 1000:1, with the proviso that said first gas and said second component are not water vapor.

2. The preparation of claim 1, wherein said second component comprises a fluorocarbon and said first gas is a nonfluorocarbon.

3. The preparation of claim 2, wherein said first gas comprises nitrogen, oxygen, carbon dioxide, or a mixture thereof.

4. The preparation of claim 2, wherein:

said microbubbles are in a liquid medium and have a first average diameter;

the ratio of said first gas to said second component in said microbubbles is at least 1:1; and

said microbubbles are adapted to shrink in said medium as a result of loss of said first gas through said membrane to a second average diameter of less than about 75% of said first diameter and then remain stabilized at or about said second diameter for at least about 1 minute as a result of a gas osmotic pressure differential across said membrane.

5. The preparation of claim 4, wherein said liquid medium contains gas or gases dissolved therein with a gas tension of at least about 700 mm Hg, wherein said first diameter is at least about 5 μm, and wherein the tension of the gas or gases dissolved in said medium is less than the pressure of the same gas or gases inside said microbubbles.

6. The preparation of claim 4, wherein said first diameter is at least about 10 μm and said second diameter is between about 1 μm and 6 μm.

7. The preparation of claim 1, wherein said second component has an average molecular weight at least about 4 times that of said first gas.

8. The preparation of claim 1, wherein said molar ratio of said first gas to said second component is from about 1:10 to about 500:1.

9. The preparation of claim 1, wherein said second component comprises a fluorocarbon and said first gas is a nonfluorocarbon.

10. The preparation of claim 9, wherein said second component comprises at least two fluorocarbons.

11. The preparation of claim 9, wherein said second component comprises a perfluorocarbon.

12. The preparation of claim 1, wherein both said first gas and said second component comprise fluorocarbons.

13. The preparation of claim 1, wherein said second component has a water solubility of not more than about 0.5 mM at 25° C. and one atmosphere, and wherein said first gas has a water solubility at least about 10 times greater than that of said second component.

14. The preparation of claim 1, wherein the permeability of the membrane to said first gas is at least about 5 times greater than the permeability of said membrane to said second component.

15. The preparation of claim 1, further comprising:

a liquid in said container in admixture with said microbubbles, wherein said container further comprises means for transmission of sufficient ultrasonic energy to said liquid to permit formation of said microbubbles by sonication.

16. The preparation of claim 15, wherein said means for transmission comprises a flexible polymer material having a thickness less than about 0.5 mm.

17. The preparation of claim 1, wherein said membrane is a surfactant.

18. The preparation of claim 17, wherein said surfactant comprises a non-Newtonian viscoelastic surfactant.

19. The preparation of claim 17, wherein said surfactant is a carbohydrate.

20. The preparation of claim 19, wherein said carbohydrate is a polysaccharide.

21. The preparation of claim 17, wherein said surfactant is a fatty acid ester of a sugar.

22. The preparation of claim 17, wherein said surfactant is sucrose stearate.

23. The preparation of claim 17, wherein said surfactant is a phospholipid.

24. The preparation of claim 1, wherein said membrane is solid or semi-solid.

25. The preparation of claim 1, wherein said membrane is a proteinaceous material.

26. The preparation of claim 25, wherein said proteinaceous material is albumin.

27. The preparation of claim 2, wherein:

said microbubbles have a first average diameter;

the ratio of said first gas to said second component in said microbubbles is at least 1:1; and

said microbubbles are adapted to shrink in blood in vivo as a result of loss of said first gas through said membrane to a second average diameter of less than about 75% of said first diameter and then remain stabilized at or about said second diameter for at least about 1 minute as a result of a gas osmotic pressure differential across said membrane.

28. The preparation of claim 27, wherein said first diameter is at least about 5 μm, and wherein the tension of the gas or gases dissolved in said blood is less than the pressure of the same gas or gases inside said microbubbles.

29. The preparation of claim 27, wherein said first diameter is at least about 10 μm and said second diameter is between about 1 μm and 6 μm.

30. The preparation of claim 27, wherein said second component has an average molecular weight at least about 4 times that of said first gas.

31. The preparation of claim 27, wherein said molar ratio of said first gas to said second component is from about 1:10 to about 500:1.

32. The preparation of claim 27, wherein said second component comprises a fluorocarbon and said first gas is a nonfluorocarbon.

33. The preparation of claim 32, wherein said second component comprises at least two fluorocarbons.

34. The preparation of claim 32, wherein said second component comprises a perfluorocarbon.

35. The preparation of claim 27 wherein both said first gas and said second component comprise fluorocarbons.

36. The preparation of claim 1, wherein said microbubbles contain as said first gas, or as said second component, or respectively as said first gas and said second component, gaseous perfluorobutane and perfluorohexane in a ratio from about 1:10 to about 10:1.

37. The preparation of claim 1, wherein said microbubbles contain as said first gas, or as said second component, or respectively as said first gas and said second component, gaseous perfluorobutane and perfluoropentane in a ratio from about 1:10 to about 10:1.

38. The preparation of claim 4, wherein said medium is aqueous.

39. A kit for use in preparing microbubbles, comprising:

a sealed container;

a liquid in said container;

a surfactant in said container; and

a fluorocarbon gas in said container, wherein said liquid, said surfactant, and said fluorocarbon gas are together adapted to form microbubbles upon the application of energy to the sealed container.

40. The kit of claim 39, further comprising

means in said container for permitting transmission of sufficient external ultrasonic energy to said liquid to form microbubbles in said container.

41. The kit of claim 40, wherein said means for transmission comprises a flexible polymer membrane having a thickness less than about 0.5 mm.

42. The kit of claim 39, further comprising:

a nonfluorocarbon gas in said container, wherein the molar ratio of said nonfluorocarbon gas to said fluorocarbon gas is from about 1:10 to about 1000:1, with the proviso that said nonfluorocarbon gas is not water vapor.

43. A kit for use in preparing microbubbles, comprising:

a container;

dried liquid-soluble void-containing structures in said container, said void-containing structures defining voids having an average diameter less than about 100 μm;

a liquid suitable for in vivo injection in which said void-containing structures are substantially soluble;

a gas in said voids, wherein said gas is the vapor of a non-aqueous material that is a liquid at 37° C.; and

a surfactant, wherein said void-containing structures, said gas, and said surfactant are together adapted to form microbubbles upon addition to said container of said liquid.

44. The kit of claim 43, wherein said void-containing structures comprise at least in part said surfactant.

45. The kit of claim 43, wherein said surfactant is a non-Newtonian viscoelastic surfactant.

46. The kit of claim 43, wherein said surfactant is a fatty acid ester of a sugar.

47. The kit of claim 43, wherein said surfactant is a phospholipid.

48. The kit of claim 43, wherein said void-containing structures are proteinaceous.

49. The kit of claim 43, wherein said void-containing structures are formed of a carbohydrate.

50. The kit of claim 43, wherein said gas is a fluorocarbon.

51. The kit of claim 43, wherein said gas comprises perfluorohexane.

52. The kit of claim 43, wherein said void-containing structures comprise spray dried microspheres.

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The foregoing description details certain preferred embodiments of the present invention and describes the best mode contemplated. It will be appreciated, however, that no matter how detailed the foregoing appears in text, the invention can be practiced in many ways and the invention should be construed in accordance with the appended Claims and any equivalents thereof.

What is claimed is:

1. A microbubble preparation, comprising:

an aqueous medium containing a plurality of microbubbles, said microbubbles comprising:

a generally spherical microbubble membrane;

a first gas and a second component contained within said membrane, wherein said second component comprises the vapor of a compound that is a liquid at 37° C. and 760 mm Hg but which has a vapor pressure of at least 75 mm Hg at 37° C., wherein the first gas and the second component are respectively present in a molar ratio of about 1:100 to about 1000:1, with the proviso that said first gas and said second component are not water vapor.

2. The preparation of claim 1, wherein said second component comprises a fluorocarbon and said first gas is a nonfluorocarbon.

3. The preparation of claim 2, wherein said first gas comprises nitrogen, oxygen, carbon dioxide, or a mixture thereof.

4. The preparation of claim 2, wherein:

said microbubbles are in a liquid medium and have a first average diameter;

the ratio of said first gas to said second component in said microbubbles is at least 1:1; and

said microbubbles are adapted to shrink in said medium as a result of loss of said first gas through said membrane to a second average diameter of less than about 75% of said first diameter and then remain stabilized at or about said second diameter for at least about 1 minute as a result of a gas osmotic pressure differential across said membrane.

5. The preparation of claim 4, wherein said liquid medium

14. The preparation of claim 1, wherein the permeability of the membrane to said first gas is at least about 5 times greater than the permeability of said membrane to said second component.

15. The preparation of claim 1, further comprising:

a liquid in said container in admixture with said microbubbles, wherein said container further comprises means for transmission of sufficient ultrasonic energy to said liquid to permit formation of said microbubbles by sonication.

16. The preparation of claim 15, wherein said means for transmission comprises a flexible polymer material having a thickness less than about 0.5 mm.

17. The preparation of claim 1, wherein said membrane is a surfactant.

18. The preparation of claim 17, wherein said surfactant comprises a non-Newtonian viscoelastic surfactant.

19. The preparation of claim 17, wherein said surfactant is a carbohydrate.

20. The preparation of claim 19, wherein said carbohydrate is a polysaccharide.

21. The preparation of claim 17, wherein said surfactant is a fatty acid ester of a sugar.

22. The preparation of claim 17, wherein said surfactant is sucrose stearate.

23. The preparation of claim 17, wherein said surfactant is a phospholipid.

24. The preparation of claim 1, wherein said membrane is solid or semi-solid.

25. The preparation of claim 1, wherein said membrane is a proteinaceous material.

26. The preparation of claim 25, wherein said proteinaceous material is albumin.

27. The preparation of claim 2, wherein:

said microbubbles have a first average diameter;

the ratio of said first gas to said second component in said microbubbles is at least 1:1; and

said microbubbles are adapted to shrink in blood in vivo as a result of loss of said first gas through said mem-

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the interchamber seal into the powder-containing chamber. The plunger motion was stopped when all the water was in the powder chamber. The syringe was agitated to dissolve the powder. Excess gas and any large bubbles were expelled by holding the syringe, needle end up, and further depressing the plunger. The solution containing numerous stabilized microbubbles (as observed by light microscopy) was then expelled from the syringe by depressing the plunger to its limit.

The foregoing description details certain preferred embodiments of the present invention and describes the best mode contemplated. It will be appreciated, however, that no matter how detailed the foregoing appears in text, the invention can be practiced in many ways and the invention should be construed in accordance with the appended claims and any equivalents thereof.

What is claimed is:

1. A method for imaging an object or body part or body cavity, comprising the steps of:

introducing into said object or body part or body cavity a microbubble preparation comprising a first gas, a second gas, a membrane forming material, and a liquid, wherein said first gas and said second gas are present in a molar ratio of about 1:100 to about 1,000:1, and wherein said first gas has a vapor pressure of at least about (760−x) mm Hg at 37° C., where x is the vapor pressure of the second gas at 37° C., and wherein said vapor pressure of each of said first and second gases is greater than about 75 mm Hg at 37° C., and the boiling point of at least one said second gas at atmospheric pressure is greater than about 37° C., with the proviso that said first gas and said second gas are not water vapor, wherein said first and second gases are surrounded with said membrane forming material; and

imaging at least a portion of said object or body by ultrasound or magnetic resonance.

2. The method of claim 1, wherein said object or body is a vertebrate and said preparation is introduced into the vasculature or body cavity of said vertebrate.

3. The method of claim 1, wherein said membrane forming material is a surfactant.

4. The method of claim 3, wherein said surfactant is a phospholipid.

combining said composition with a liquid in which said microspheres are soluble and said microspheres are dissolved in said liquid whereby the gases in said microspheres form microbubbles that are surrounded by said surfactant.

7. The method of claim 2, further comprising the step of preparing said microbubble preparation outside of said vertebrate prior to said introducing step.

8. The method of claim 7, further comprising the step of:

initially forming microbubbles having a first average diameter wherein the initial ratio of said first gas to said second gas in said microbubbles is at least about 1:1, wherein said microbubbles are adapted to shrink in blood in vivo as a result of loss of said first gas through said membrane to a second average diameter of less than about 75% of said first diameter and then remain stabilized at or about said second diameter for at least about 1 minute.

9. The method of claim 8, wherein said first diameter is at least about 5 μm, and wherein the tension of the gas or gases dissolved in said blood is less than the pressure of the same gas or gases inside said microbubble.

10. The method of claim 8, wherein said first diameter is at least about 10 μm and said second diameter is between about 1 μm and 6 μm.

11. The method of claim 8, wherein said second gas has an average molecular weight at least about 4 times that of said first gas.

12. The method of claim 8, wherein said second gas has a vapor pressure less than about 750 mm Hg at 37° C.

13. The method of claim 8, wherein said molar ratio of said first gas to said second gas is from about 1:10 to about 500:1.

14. The method of claim 8, wherein said second gas comprises a fluorocarbon and said first gas is a nonfluorocarbon.

15. The method of claim 8, wherein said second gas comprises at least two fluorocarbons.

16. The method of claim 8, wherein said second gas comprises a perfluorocarbon.

17. The method of claim 8, wherein both said first gas and said second gas comprise fluorocarbons.

18. The method of claim 8, wherein said second gas is perfluorohexane.

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[illegible] microbubbles (as observed by light microscopy) was then expelled from the syringe by depressing the plunger to its limit.

The foregoing description details certain preferred embodiments of the present invention and describes the best mode contemplated. It will be appreciated, however, that no matter how detailed the foregoing appears in text, the invention can be practiced in many ways and the invention should be construed in accordance with the appended claims and any equivalents thereof.

What is claimed is:

1. A method for forming microbubbles, comprising the steps of:

providing a first gas, a second component, a membrane forming material, and a liquid, wherein said first gas and said second component are present in a molar ratio of about 1:100 to about 1,000:1, and wherein said second component comprises vapor of a compound that is liquid at 37° C. and 760 mm Hg but which has a vapor pressure of at least 75 mm Hg at 37° C. with the proviso that said first gas and said second component are not water vapor; and

surrounding said first gas and said second component with said membrane forming material to form microbubbles in said liquid.

2. The method of claim 1, wherein said membrane forming material is a surfactant.

3. The method of claim 2, wherein said membrane forming material comprises a non-Newtonian surfactant.

4. The method of claim 1, further comprising the steps of:

initially forming microbubbles having a first average diameter wherein the initial ratio of said first gas to said second component in said microbubbles is at least about 1:1;

contacting said microbubbles having a first average diameter with a liquid medium;

shrinking said microbubbles in said medium as a result of loss of said first gas through said membrane; and then

stabilizing said microbubbles at a second average diameter of less than about 75% of said first diameter for a period of at least one minute.

5. The method of claim 4, wherein said microbubbles are stabilized at said second diameter by:

[illegible] that are surrounded by said surfactant.

8. The method of claim 7, wherein said void-containing structures are microspheres.

9. The method of claim 7, wherein said microbubbles contain a first gas and a second halogenated gas respectively present in a molar ratio of from about 1:100 to about 1000:1.

10. A method for imaging an object or body part or body cavity, comprising the steps of:

introducing into said object or body or body part or body cavity a microbubble preparation according to claim 1; and then

imaging at least a portion of said body by ultrasound or magnetic resonance.

11. The method of claim 10, wherein said body is a vertebrate and said preparation is introduced into the vasculature or body cavity of said vertebrate.

12. The method of claim 10, wherein said preparation is a preparation as defined in claim 2.

13. The method of claim 10, wherein said preparation is a preparation as defined in claim 7.

14. The method of claim 10, wherein said preparation is a preparation as defined in claim 8.

15. The method of claim 10, further comprising the step of preparing said microbubble preparation prior to said introduction according to the method of claim 1.

16. The method of claim 10, further comprising the step of preparing said microbubble preparation prior to said introduction according to the method of claim 4.

17. The method of claim 10, further comprising the step of preparing said microbubble preparation prior to said introduction according to the method of claim 5.

18. The method of claim 10, further comprising the step of preparing said microbubble preparation prior to said introduction according to the method of claim 7.

19. A method for producing microbubbles having increased in-vial stability, comprising the steps of:

spray drying a liquid formulation containing a biocompatible film-forming material to form a microsphere powder therefrom;

combining the microspheres with a gas osmotic agent and storing the microspheres in a container with the gas osmotic agent; and then

mixing an aqueous phase with the powder, wherein said powder substantially dissolves in the aqueous phase to form microbubbles.

20. The method of claim 19, wherein said film-forming